REMARKS

Favorable reconsideration is respectively requested in foregoing amendments and following remarks.

Claims 1, 5 and 13 have been amended to incorporate the limitations of claims 86, 87 and 88. Claims 83-88 are cancelled.

Although the pending action is final, it is respectively submitted that the foregoing amendment should be entered, since the amendments were previously pending and examined prior to the issuance of the final rejection.

Claims 1-20 and 63-88 are rejected under 35 U.S.C. 103 as being unpatentable over Negoro et al., US Patent 5,258,382, in view of Muller et al., US Patent 5,858,410. This ground of rejection is again respectively traversed.

(1) Although the Examiner again says that the present invention is obvious over the cited Negoro et al in view of Muller et al, and that Muller et al clearly teach a range of 10 nm to 1,000 nm corresponding to 0.01 to 1 micron, which falls just outside the claimed range as amended, it appears to the Applicant that the Examiner misunderstands or confuses the solubility of a solid compound in water with the dissolution rate (dissolution speed) of the compound from the preparation, as if a higher solubility in water naturally results in a faster dissolving out of the compound from a preparation. These characteristics are not the same. Further, it appears to the Applicant that the Examiner has a misconception that the smaller size of a solid compound, the higher solubility of the compound in water, as well as the higher dissolution speed of the compound from a preparation. It has never been taught or suggested by the cited references that the smaller the size of a solid compound, the higher the speed of dissolving out of the compound from a pharmaceutical preparation containing the same.

The present inventors first noticed that the solubility of AS-3201 in water disclosed in Negoro et al is extremely low, only a few or several micrograms per ml at a lower pH range, and that the blood concentration of AS-3201 varies largely depending on the subjects. The present inventors have intensively studied to increase the dissolution speed of AS-3201 from a pharmaceutical preparation. As a result, the present inventors have found that when the solid

AS-3201 is micronized to a mean particle size of from about 0.5 μm to less than about 20 μm, preferably from above 1 μm to less than about 20 μm, and a pharmaceutical preparation is prepared using this specifically micronized AS-3201, the preparation can exhibit excellent dissolution speed when orally administered. That is, when a dissolution percentage of AS-3201 from the composition is measured according to the Paddle method, 50% or more of the AS-3201 in the composition is dissolved within 15 minutes from the start of the method, and thus the pharmaceutical composition of AS-3201 shows excellent bioavailability compared to Negoro et al..

(2) Although the Examiner says that the present invention is obvious over Negoro et al, because Negoro et al disclose a solid dosage form of pharmaceutical composition, Negoro et al do not teach or suggest a solid composition of micronized AS-3201 having the claimed specific average particle size. Moreover, Negoro et al never teach or suggest that such a specific solid composition exhibits the excellent dissolution rate (speed) of AS-3201 from the composition when orally administered, according to the claims. It was experimentally proved by the comparative experiments in the Declaration by Mr. Mamoru OHASHI as filed that the solid composition of the present invention exhibits an unexpectedly excellent dissolution speed of AS-3201 when administered in comparison with the composition disclosed in Negoro et al.

(3) As to the secondary Muller et al reference, the Examiner says that Muller et al discloses that increased surface area through reduction of particle size allows a faster rate of dissolution, hence it would be obvious to the skilled person to reduce the particle size of the active compound to less than 20 microns. However, again, it should be recognized that the dissolution of a solid compound in water is not the same as the speed of a compound dissolving out of a composition. In addition, Muller et al does not teach that a solid compound having increased surface area exhibits a faster rate of dissolving out from a composition and has higher bioavailability.

Muller et al disclose merely that an insoluble compound having an average diameter of 10 nm to 1,000 nm shows sparing solubility in water, aqueous media and/or organic solvents. Muller et al do not teach that the compound having such a particularly small particle size shows

faster dissolving out from the composition when administered. It should further be noted that Muller et al disclose preparing an active compound having particularly smaller particle size in the nanometer range. In this respect, the Examiner pointed out that the upper limit of 1,000 nm in Muller et al. corresponds to 1 micron, which falls within range of the instant invention. However, the claims as amended define over Muller, by claiming a lower limit of above 1 micron. Moreover, it should be noted that the main range of Muller et al is much smaller than 1 micron. This means that the invention of Muller et al and the present invention are substantially different in basic idea. The basic idea of Muller et al is to provide a drug carrier of pure active (insoluble) compound of high saturation solubility and high rate of dissolution (in water) to be able to give a suspension having a high saturation of an active compound which is suitable for injection, e.g., intravenous injection. On the other hand, the basic idea of the present invention is to provide a pharmaceutical composition which can rapidly dissolve out the active compound, hardly soluble AS-3201, from the composition within a body when orally administered. This characteristic does not necessarily have a direct relation with the property of a high saturation in water or a high rate of dissolution in water.

The above points will be explained in more detail below.

The Examiner pointed out that "Muller discloses that the dissolution rate increases as the particle surface area increases in accordance with the Noyes-Whitney law. As a results of increased dissolution rate increases bioavailability (col. 1, lines 44-50)". However, this passage mentions merely a general law - it does not indicate the invention of Muller et al. The Examiner said by referring to Example 8 of Muller et al. (col. 14, lines 49-55 and figures), the Muller et al. reference teaches a particle in the range of 10 to 1,000 nm and 65% dissolution rate within ten minutes. However, this statement is incorrect. Example 8 of Muller et al. merely shows that dissolution over saturation solubility (super saturation) according to Ostwald-Freundlich equation was achieved.

That is, as is mentioned, Muller et al., col. 5, line 66 to col. 6, line 18, "an increase in the saturation solubility when the particle size is decreased is postulated in the Ostwald-Freundlich equation, but this does not have an effect on particles in the micrometer range." The desired

suspension suitable for intravenous injection of Muller et al. could be obtained only by grinding the active compound to nanometer size particles with a specific means, but not in micrometer size particles.

In Muller et al., the experiments of dissolution properties of the compound are done only in Examples 7 and 8.

In Example 7, wherein the comparison of the saturation solubility of microparticles and nanosuspensions was done, it is mentioned that the nanosuspension showed a higher saturation solubility (Csm 3.29 mg/1 and 3,52 mg/1) than that of microparticles (Csm 1.97 mg/1). It is also mentioned therein that such a property (increase in the saturation solubility with decreasing particle size) described in the Ostwald-Freundlich equation. It is also mentioned in Muller et al. that the Ostwald-Freundlich equation is not applied to the particles in a micrometer size (cf. Muller et al., col. 6, lines 1-7).

In Example 8, the dissolution properties of nanosuspensions were compared with microparticles, and it is mentioned that the sample adding nanosuspension (i.e. said sample being prepared by adding nanosuspension to a solution saturated with microparticles) showed increased dissolution of the particles, but the sample adding microparticles (i.e. a sample prepared by adding microparticles to a solution saturated with microparticles) did not show any increase of dissolution of the particles. This means that nanosuspension can be further dissolve in a solution saturated with microparticles, in other words, it proves the third advantage of nanosuspensions as mentioned in Muller et al., col. 1, line 66 to col. 2, line 6, that is, a reduction in the injection volume of drugs can be achieved by formulation as a nanosuspension.

As is clear from the above explanation, Muller et al. disclose that nanometer size particles show increased saturation solubility and can be used for a suspension suitable for intravenous injection which can contain an increased amount of the active drug, but Muller et al. do not teach or even suggest that a micronized (hardly soluble or insoluble) compound having the specified micron order particle size (like in the range of above 1 micron to 20 microns) can exhibit such excellent properties of excellent dissolution rate (speed) of the active compound from the composition when orally administered.

(4) Finally, it should also be noted that contrary to the Examiner's position of "it is known that decreased particle size gives increased dissolution rate and then results in increased bioavailability", it is known that the decrease of particle size does not necessarily give increased bioavailability. It is described, for example, in U.S. Patent 4,840,799 (see attached copy of said U.S. patent) as follows.

"It is well known that bioavailability particularly of slightly soluble active compounds is highly dependent on the particle size of the active compound or its specific surface area. The greater the area of the particle the greater the solubility rate in gastrointestinal juice prior to absorption through the mucous membranes. It is, however, also known that bioavailability can not always be improved as desired, only by preparing the compound in a very fine particulate form (micronizing). These difficulties are particularly pronounced when the substance in spite of a small particle size is released during a long time period and over a long distance in the gastrointestinal tract." (cf. in U.S.P. 4,840,799, col. 1, lines 25-37)

In summary, all independent claims 1, 5 and 13 now recite a range of particle sizes of above 1 micron to less than about 20 microns. This range defines over the upper range of Negoro et al. Although the declaration provides for a lower limit of 1.5 microns, one skilled in the art would reasonable expect a particle size of above 1 micron to exhibit the same properties as the 1.5 micron particle size. Accordingly, it is reasonable to consider the declaration to be commensurate with the scope of the claims.

Accordingly, even though the primary Negoro et al reference are considered together with the secondary Muller et al reference, the specific fast-dissolving pharmaceutical composition of the present invention would have never been predicted. Thus, the Applicant respectfully submits that the present invention is patentable over the cited references.

Claims 61-62 are also rejected under 35 U.S.C. 103 as unpatentable over Negoro et al. in view of Muller et al. in further view of Schmeider et al., US Patent 5,356,636.

It is respectively submitted that this ground of rejection has been overcome, by overcoming the rejection of the independent claim, for the reasons set forth above.

In view of the foregoing, favorable reconsideration and allowances respectively solicited.

Respectfully submitted,

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